REMARKS

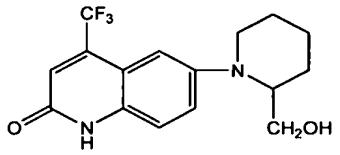
The requisite fee for a three-month extension of time and any other fees that may be due in connection with the filing of this paper or with this application should be charged to Deposit Account No. 02-1818. If a Petition for Extension of Time is needed, this paper is to be considered such Petition. A Declaration pursuant to 37 C.F.R. § 1.132 is provided.

Claims 1-23 and 25-45 are pending. Claim 24 is cancelled without prejudice or disclaimer and claim 45 is added. Claim 1 is amended to more distinctly claim the subject matter by separating the definition of substituents R^3 and R^4 and deleting hydrogen as an alternate selection in the definition of R^3.

Claims 2-8 and 13 and 22 are amended to conform to claim 1 in light of the amendments herein. Claim 14 is amended to depend from claim 1. Claims 1-23 and 25-44 are amended to correct minor typographical or formatting errors. Basis for new claim 45 is found at paragraph [0154] on pages 43-44. No new matter is added.

I. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §102(b)

Claims 1-44 are rejected under 35 U.S.C. § 102(b) as anticipated by W02001016108 (Zhi *et al.*), because this reference allegedly describes the compound:



as an androgen receptor modulator, and the Examiner alleges that this compound is within the scope of the instant claims and therefore anticipates all claims.

Reconsideration of the grounds for the rejection respectfully is requested in view of the amendments herein and the following remarks.

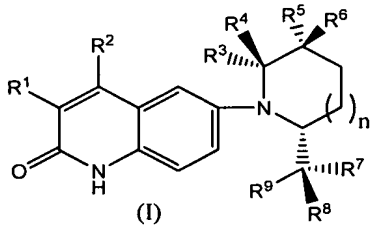
RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is

disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 1 recites compounds of the structure

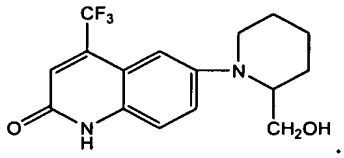


(I)

where R^3 is selected from the group of C_1-C_4 aliphatic, C_1- C_4 haloaliphatic, C_1-C_4 heteroaliphatic, optionally substituted aryl and heteroaryl; R^4 is selected from the group of hydrogen, C_1-C_4 aliphatic, C_1- C_4 haloaliphatic, C_1-C_4 heteroaliphatic, optionally substituted aryl and heteroaryl; and the other substituents are as defined in the claim. Claims 2-23 and 25-44 ultimately depend from claim 1 and include every limitation thereof.

Disclosure of Zhi *et al.* and differences from the claimed subject matter

This reference describes almost 600 compounds. Of the compounds described in Zhi *et al.*, many are not structurally similar to the instantly claimed compounds. Zhi *et al.* does disclose several bicyclic compounds substituted with a pendant ring, including the compound cited by the Examiner, in which the ring is attached to the bicyclic core by a nitrogen atom of the heterocycle, one carbon atom adjacent to the nitrogen atom of the pendant ring is substituted with the moiety CH_2OH and the other carbon atom adjacent to the nitrogen atom of the pendant ring is substituted with hydrogen:



All of the bicyclic compounds with a pendant ring in Zhi *et al.* include only a single substituent on the 6-cycloamino ring – one of the carbon atoms adjacent to the nitrogen heteroatom includes only hydrogen as a substituent.

The instantly claimed compounds differ from the compounds of Zhi *et al.* in that the instant compounds include a second non-hydrogen substituent on the 6-cycloamino ring (substituent R^3 cannot be hydrogen).

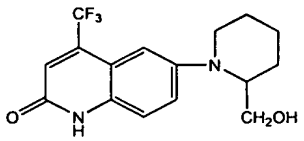
ANALYSIS

The bicyclic compounds of Zhi *et al.* include only a single functional group on the pendant 6-cycloamino ring – one of the carbon atoms adjacent to the nitrogen heteroatom includes only hydrogen as a substituent. The compounds as instantly claimed include a non-hydrogen substituent on each carbon atom adjacent to the nitrogen atom of the pendant heterocyclic ring. Therefore, neither the cited bicyclic compound nor any compound of Zhi *et al.* is within the scope of the instant claims.

Accordingly, for at least these reasons, Zhi *et al.* does not disclose every element of independent claim 1. Claims 2-23 and 25-44 ultimately depend from claim 1 and include every limitation thereof. Thus, Zhi *et al.* does not disclose every element of claims 1-23 and 25-44. Therefore, Zhi *et al.* does not anticipate of any of claims 1-23 and 25-44.

II. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §102(e)

Claims 1-44 are rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Pat. Nos. 6,566,372 (Zhi *et al.*) and 6,964,973 (Zhi *et al.*) because each reference allegedly describes the compound:



as an androgen receptor modulator, and the Examiner alleges that the compound is within the scope of the claims and therefore anticipates all claims.

Reconsideration of the grounds for the rejection respectfully is requested in view of the amendments herein and the following remarks.

RELEVANT LAW

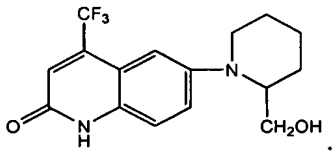
See related section above.

THE CLAIMS

The claims are discussed in a related section above.

Disclosure of the cited art and differences from the claimed subject matter

U.S. Pat. No. 6,964,973 is a divisional of U.S. Pat. No. 6,566,372 and thus the specifications are the same. Each reference describes substituted bicyclic androgen and progesterone receptor modulator compounds, among which is the cited compound:



All of the bicyclic compounds with a pendant ring U.S. Pat. Nos. 6,566,372 and 6,964,973 include only a single substituent on the 6-cycloamino ring – one of the carbon atoms adjacent to the nitrogen heteroatom includes only hydrogen as a substituent. The instantly claimed compounds differ from the compounds described in U.S. Pat. Nos. 6,566,372 and 6,964,973 in that the instant compounds include a second non-hydrogen substituent on the 6-cycloamino ring (substituent R^3 cannot be hydrogen).

ANALYSIS

The bicyclic compounds described in U.S. Pat. Nos. 6,566,372 and 6,964,973 include only a single functional group on the pendant 6-cycloamino ring – one of the carbon atoms adjacent to the nitrogen heteroatom includes only hydrogen as a substituent. The compounds as instantly claimed include a non-hydrogen substituent on each carbon atom adjacent to the nitrogen atom of the pendant heterocyclic ring. Therefore, neither the compound of U.S. Pat. Nos. 6,566,372 and 6,964,973 cited by the Examiner nor any compound of U.S. Pat. Nos. 6,566,372 and 6,964,973 is within the scope of the instant claims. U.S. Pat. Nos. 6,566,372 and 6,964,973 do not describe any compound that is within the scope of the instant claims.

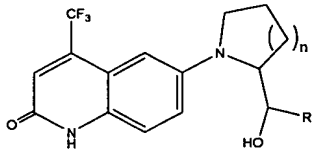
Accordingly, for at least these reasons, U.S. Pat. Nos. 6,566,372 and 6,964,973 do not disclose every element of independent claim 1. Claims 2-23 and 25-44 ultimately depend from claim 1 and include every limitation thereof. Thus, U.S. Pat. Nos. 6,566,372 and 6,964,973 do not disclose every element of claims 1-23 and 25-44. Therefore, U.S. Pat. Nos. 6,566,372 and 6,964,973 do not anticipate any of claims 1-23 and 25-44.

UNOBVIOUSNESS

Notwithstanding the fact that none of the Zhi *et al.* references (W02001016108, U.S. Pat. No. 6,566,372 and U.S. Pat. No. 6,964,973) discloses any compound within the scope of the instant claims, in order to advance prosecution of this application, Applicant also respectfully submits that, as shown in the attached Declaration from Dr. Zhi, an inventor of the claimed subject matter, when the properties of the compounds of the instant claims are compared to the structurally closest analogs of Zhi *et al.*, the compounds within the scope of the instant claims demonstrate properties that are different from the closest prior art compounds and that are not taught or suggested in Zhi *et al.* As discussed in more detail

below, the instantly claimed compounds are unobvious over the teachings of W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372.

Among the compounds described in W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372 are compounds of the formula



where R is trifluoromethyl and n is 2 (Compounds 437 and 438) and R is trifluoromethyl and n is 1 (Compounds 450 and 451). All of the compounds described in W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372 that have some structural similarity to the instantly claimed compounds include a carbon atom adjacent to the nitrogen atom in the pendant pyrrolidino or piperidino ring that includes only hydrogen as a substituent. None of the compounds described in W02001016108 or U.S. Pat. Nos. 6,964,973 and 6,566,372 includes a non-hydrogen substituent on both carbon atoms adjacent to the nitrogen atom in the pendant pyrrolidino or piperidino ring.

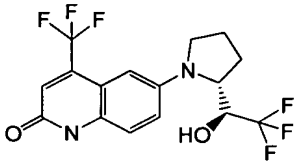
Thus, the compounds as instantly claimed include non-hydrogen substituents on each carbon atom adjacent to the nitrogen atom in the pendant pyrrolidino or piperidino ring. None of the compounds described in W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372 with a pendent substituted 6-(2-methyl-pyrrolidin-1-yl) or 6-(2-methylpiperidin-1-yl) ring includes these features, and there is no teaching or suggestion in W02001016108 or U.S. Pat. Nos. 6,964,973 and 6,566,372 to modify the compounds described therein to arrive at the compounds as instantly claimed. None of W02001016108, U.S. Pat. No. 6,964,973 or U.S. Pat. No. 6,566,372 teaches or suggests selecting from among the genus of compounds described therein 6-(pyrrolidin-1-yl)-quinolin-2(1*H*)-ones or 6-(piperidin-1-yl)-quinolin-2(1*H*)-ones and modifying the described compounds by replacing an unsubstituted carbon atom adjacent to the nitrogen atom of a pyrrolidinyl or piperidinyl ring with a carbon atom that contains at least one non-hydrogen substituent, such as a C_1-C_4 alkyl substituent. Accordingly, there is no teaching or suggestion in W02001016108 or U.S. Pat. Nos. 6,964,973 and 6,566,372 that would have led the skilled artisan to do what Applicant has done.

DECLARATION

The DECLARATION of Dr. Lin Zhi provides data that shows that when the closest compounds of Zhi *et al.* are compared to the compounds of formula I of claim 1, the instant compounds exhibit properties not taught or suggested by Zhi *et al.* In particular, compounds

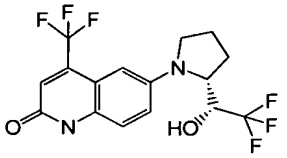
within the scope of claim 1 were compared to the compounds of Zhi *et al.* that are the closest structural analogs of formula I. The DECLARATION demonstrates that compounds of formula I of claim 1 in which the carbon atom adjacent to the nitrogen atom of pendant heterocyclic ring includes a non-hydrogen substituent (at the position corresponding to R^3 of formula I of claim 1) exhibit enhanced efficacy compared to the compounds of Zhi *et al.*

According to Dr. Zhi, an inventor of the claimed subject matter, of the compounds that have some structural similarity, Compounds 450 and 451 of Zhi *et al.* of W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372 (described in Example 200), which have the following structures:



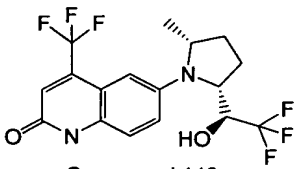
US 6,566,372
Compound 450

and



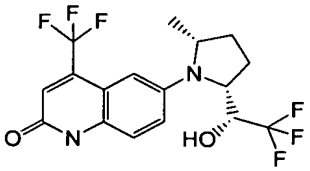
US 6,566,372
Compound 451

are most similar to claimed compounds in the instant application (see the attached Declaration). Compounds 450 and 451 of Zhi *et al.* (W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372) include only a single functional group on the 6-cycloamino ring – one of the carbon atoms adjacent to the nitrogen heteroatom includes only hydrogen as a substituent. The instantly claimed compounds differ from the compounds of Zhi *et al.* in that the instant compounds include a secondary functional group on the 6-cycloamino ring (substituent R^3 cannot be hydrogen). For example, Compounds 113 and 114 of the instant application, which are within the scope of the pending claims, include a methyl substituent on the carbon atom adjacent to the nitrogen atom of the heterocyclic ring:



Compound 113

and



Compound 114

The instant compounds and the compounds of Zhi *et al.* (W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372) that have some structural similarity (Compounds 450 and 451) were tested in the human androgen receptor (hAR) cotransfection assay for their ability to modulate the androgen receptor. The instantly claimed compounds and the structurally related compounds of Zhi *et al.* have excellent pharmacological activity, with an agonist efficacy of from 95% to 117% of the activity of the control AR agonist dihydroxytestosterone.

As shown in the Declaration, the instant compounds and the representative compounds of W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372 that have structural similarity also were tested in the standard Ames test for genotoxicity. When tested in the standard Ames test, the instantly claimed compounds are significantly different from the compounds of Zhi *et al.* (W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372). The tested compounds of Zhi *et al.* are toxic in the Ames test after metabolic activation. The instantly claimed compounds are not toxic in the Ames test after metabolic activation.

In the Ames test assays, the structurally related representative compounds of W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372 (Compounds 450 and 451) are highly toxic after the compounds were treated with S9, a metabolic enzyme. In contrast, Compounds 113 and 114 of the instant application, which include a methyl group as a secondary functional group on the 6-cycloamino ring, are negative in the Ames test after metabolic activation. As shown in the Declaration, testing of additional compounds demonstrated that analogs of compounds of formula I of claim 1 that lack the secondary functional group on the 6-cycloamino ring are toxic after metabolic activation (have a strong positive activity in the Ames test), while compounds within the scope of the claims, with a secondary functional group on the 6-cycloamino ring (Compounds 128 and 129), are totally negative in the Ames test after metabolic activation. All of the instantly claimed compounds of formula I include a secondary functional group on the 6-cycloamino ring, such as a methyl group. Accordingly, it can be inferred that because all of the instantly claimed compounds include a secondary functional group on the 6-cycloamino ring that they will have similar activity and will be negative in the Ames test. Thus, compounds of formula I of claim 1 of the instant application have properties that differ significantly from the closest compounds described in Zhi *et* al. (W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372).

The compounds of W02001016108 and U.S. Pat. Nos. 6,964,973 and 6,566,372, which do not have a secondary functional group on the 6-cycloamino ring, are toxic following metabolic activation. A compound that is toxic is not efficacious. The compounds of formula I of claim 1 of the instant application, which include a secondary functional group on the 6-cycloamino ring (*e.g.*, Compounds 113, 114, 128 and 129), are not toxic, as demonstrated in the Ames test. Thus, compounds of formula I of instant claim 1, which are not toxic, exhibit enhanced efficacy compared to the compounds of Zhi *et al.* Therefore, the instant compounds are unobvious over the teachings of Zhi *et al.*

* * *

In view of the amendments and remarks herein, reconsideration and allowance respectfully are requested.

Respectfully submitted,

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